UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte GEORGE BARRY KITTO and MARY SUSAN BURNETT

Appeal No. 2006-2312
Application No. 09/244,195

ON BRIEF

Before GRIMES, GREEN, and LEBOVITZ, Administrative Patent Judges.

LEBOVITZ, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to methods of initiating an immune response which is specific for HIV-1 reverse transcriptase or transactivating protein. The examiner has rejected the claims as obvious over prior art. We have jurisdiction under 35 U.S.C. § 134. We reverse.

Background

The development of an effective vaccine to prevent or treat human immunodeficiency virus (HIV) has been the subject of intense scientific research, but success has been elusive. One approach to vaccine development has been the use of

live bacterial vaccines. Specification, page 5, lines 10-17. Bacteria are genetically manipulated to express pathogen antigens (e.g., HIV gp120) which are administered to host animals with the objective to induce an immune response to the antigen. Id., page 5, lines 10-13. These studies have shown that live bacterial vaccines "are capable of eliciting both humoral and cellular immune responses" to the pathogen antigen produced by the bacterial host. Id., page 5, lines 13-17.

The application in this appeal describes live HIV bacterial vaccines that are comprised of attenuated bacterial strains engineered to express HIV antigens on their cell surface. Id., pages 5-6. In certain embodiments, attenuated Salmonella are utilized as the host. Id. These bacteria have the advantage that they can be orally administered. Id. After ingestion, they are sequestered preferentially by the intestinal mucosa, where they can induce humoral and cell-based immunity. Id., page 5, line 10-page 6, line 16. The prior art identifies several advantages of such live vaccines utilizing Salmonella or other enteric bacterial hosts:

> Live vaccines provide more efficient immunity and longer protection against infections compared to subunit or killed bacterial vaccines. There are several reasons for the higher efficacy of live bacterial vaccines (Dougan et al. 1989): i) Protection correlates with how long the vaccine is present in the body (De Libero and Kaufman, 1986). Since the bacteria persist in the intestine for very long times, they are able to confer extended immunity; ii) Unlike most currently used vaccines, bacterial vaccines may be administered orally; and iii) Several antigens may be expressed simultaneously in bacteria thus giving rise to multipurpose vaccines.

Georgiou[1], column 12, lines 47-59.

[1] Georgiou et al., (Georgiou), U.S. Pat. No. 5,348,867, issued Sept. 20, 1994

Discussion

1. Claim construction

Claims 6, 8-10, 12, and 13 are on appeal. Claim 6 is the broadest claim. It reads as follows:

> A method of initiating an immune response specific for transactivating protein or reverse transcriptase of human immunodeficiency virus type 1 (HIV-1) in an animal, said method comprises the step of:
>
> administering to said animal an attenuated bacterial host comprising a recombinant plasmid that carries a fusion protein construct, wherein said fusion protein construct comprises a gene required for surface exposure and a gene encoding said transactivating protein or reverse transcriptase of HIV-1, wherein said bacterial host can induce both cellular and humoral anti-HIV-1 immune responses in said animal.

The claimed method involves administering an attenuated bacterial host to an animal, where the host expresses a fusion protein construct that contains "a gene required for surface exposure" and "a gene encoding said transactivating protein or reverse transcriptase of HIV-1."

"[C]laims 'must be read in view of the specification, of which they are a part.'" Phillips v. AWH Corp., 415 F.3d 1303, 1315, 75 USPQ2d 1321, 1327 (Fed. Cir. 2005). "[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" Id. (internal citations omitted.) The claimed subject matter is described in the application as being useful to achieve "surface expression" of HIV antigens in host bacteria for the purpose of developing live vaccines. Specification, page 12, line 19-page 13, line 3. The bacteria are used as to deliver HIV antigens to the immune system where an immune response is induced. Id.

According to the application, a gene construct is made which encodes a fusion protein that comprises a gene for "surface exposure" linked to a gene for a "transactivating protein or reverse transcriptase of HIV-1." Id., page 15, lines 10-18. The example provided of the "surface exposure" gene is a DNA coding for the lipoprotein (lpp) signal sequence which is linked to a DNA coding for the outer membrane protein OmpA. Id., page 13, lines 4-20. Thus, we interpret "gene" to refer to the DNA which codes for a protein (e.g., lpp and OmpA).

The lpp sequence is characterized as "necessary to direct the protein construct to the outer membrane of the gram negative bacteria." Id., page 13, lines 7-9; page 20, lines 1-8. The OmpA sequence is further utilized to expose the fusion protein on the outer surface of the outer membrane of the bacterial host in which it is expressed. Id., page 13, lines 10-20. In the context of the specification, we therefore understand "surface exposure" to refer to being present on the "outer membrane" surface of bacteria. Id., page 13, line 8; page 49, lines 7-17; page 50, lines 12-page 51, line 2. Thus, we construe the phrase "gene required for surface exposure" to include coding sequences for proteins that target and expose a protein of interest to the surface of the outer cell membrane of bacteria. Our interpretation is consistent with the prior art. For example, Georgiou describes lpp and OmpA, as well as other sequences that are used to target and anchor fusion proteins on the outer surface of bacterial membranes. Georgiou, column 3, line 40-column 5, line 56.

According to claim 1, when the claimed bacterial host is administered to an animal, it "can induce both cellular and humoral anti-HIV-1 immune responses in said animal." A humoral response in the context of the specification is understood to be an

antibody response, e.g., detection of IgA. Specification, e.g., page 52. Appellant challenged the examiner's interpretation of the type of response that would be characterized as a "cellular" response.

The examiner construed the "cellular" response to include any T-cell response, including a T-cell response responsible for inducing a "humoral" (antibody) response. The examiner cited Cruse et al., Illustrated Dictionary of Immunology (1995), as supporting his position.

> Third, it is well-known in the field of immunology that B-cells produce antibody in response to activated T-helper lymphocytes ($CD4^+$). $CD4^+$ lymphocytes become activated when antigen presenting cells (e.g., macrophages) present antigens to their cell surface. There is no question in this study that strong mucosal IgA immune responses were generated. The generation of this type of immune response clearly requires a strong T-helper cell component.

Answer, paragraph spanning pages 17-18 (footnote omitted).

In the Reply Brief, Appellant rejected this construction:

> ... the Answer goes on to suggest that a humoral response necessarily includes a T-helper response and is thus really both a humoral and a cellular response as required by the claims. This argument is unsupported by the claim language itself, which clearly denotes a separate humoral and cellular response ...

Reply Brief, page 5.

The specification does not provide an express definition of either "humoral" or "cellular" response. However, the structure of independent claim 6 supports Appellant's argument that the claimed cellular response should include cells not involved in the induction of the humoral response. The examiner essentially proposes to read "humoral response" to subsume a "cellular response." In other words, if a humoral response is induced by the bacterial host, then necessarily a cellular response has also been

elicited. This construction would leave the limitation that the attenuated bacteria also elicit a "cellular" response superfluous and without meaning. In Primos v. Hunter's Specialties, 451 F.3d 841, 848, 79 USP2d 1129, 1134 (Fed. Cir. 2006), the court refused to adopt a construction that that would read two different terms to mean the same thing: "Starting with the language of claim 21, the terms 'engaging' and 'sealing' are both expressly recited in the claim and therefore 'engaging' cannot mean the same thing as 'sealing'; if it did, one of the terms would be superfluous." For this reason, we construe the cellular response to involve cells which differ from those in the humoral response.

Obviousness under 35 U.S.C. § 103

A. Hone in view of Georgiou and Thimmig

Claims 6, 8-10, 12, and 13 stand rejected under 35 U.S.C. § 103(a) as obvious over Hone[2] in view of Georgiou and Thimmig[3].

Hone describes the use of Salmonella vaccine vectors for the induction of HIV-specific mucosal and systemic immune responses. Hone, Abstract. Expression vectors were constructed which contained coding sequences for the HIV-1 gp120 antigen. Id. Two vector constructs were made. In the first, gp120 was fused in-frame with OmpA ("outer membrane protein A") to produce a chimeric protein ("OmpA::tgp120"). Id., page 205, column 1. OmpA is normally located in the bacterial cell's outer surface membrane. Georgiou, column 4, lines 62-63. By placing it in front of gp120, OmpA

[2] Hone et al. (Hone), J. Biotech., 44:203-207, 1996
[3] Thimmig et al. (Thimmig), J. Biol. Chem., 268:16528-16536, 1993

brings the attached gp120 to the surface membrane. Id., column 4, lines 19-23. The second construct prepared by Hone contained the gp120 antigen, but lacked the OmpA protein sequence. Hone, page 204, column 2. As a consequence, when the construct was expressed in an attenuated Salmonella host, the gp120 was not directed to the outer membrane, but instead, remained inside the cell. Id., Abstract; page 204, column 2.

Salmonella were transformed with the vector constructs and then orally administered to mice in order to induce an immune response to HIV gp120. Id., page 205, column 2. Mice immunized with the transformed Salmonella strain in which gp120 was localized to the outer membrane surface produced IgA in the intestinal lamina propria ("a local humoral immune response against gp120") and a "systemic humoral response" characterized by the production of serum anti-gp120 IgG. Id., page 205, Table 1; paragraph spanning pages 205-206. In contrast, mice administered the second construct in which the gp120 is expressly intracellularly, only exhibited the IgA response, but did not develop serum IgG. Id.

Georgiou describes recombinant vectors for localizing proteins of interest to the outer membrane surface of gram-negative bacteria. Georgiou, column 3, lines 40-55. The vector can include "a tripartite chimeric gene having a membrane targeting sequence, a membrane translocating sequence capable of locating a fusion protein on the outer surface and a gene segment encoding any of a variety of proteins." Id., column 3, lines 47-52. Examples include lpp (membrane targeting sequence; id., column 3, lines 57-59) fused to OmpA (membrane translocating sequence; id., column 4, lines 4-23) which is fused to a protein of interest. Id., column 2, lines 58-65.

Salmonella is described as a preferred host. Id., column 5, lines 57-61. The expression system is described as being useful for a variety of purposes, including the production of antibodies and bacterial vaccines. Id., column 6, lines 19-38; column 7, lines 30-41. In particular, Georgiou describes the use of the expression system to produce attenuated live bacterial vaccines that express the foreign antigen on the bacterial cell surface, including an example where the antigen is HIV-1 gp120. Id., column 12, line 25-column 14, line 45; column 13, lines 28-31.

HIV-1 reverse transcriptase (RT) is a dimer containing two subunits, p51 and p66. Thimmig, page 16528. Abstract. Thimmig characterized the two subunits, including their catalytic activity and substrate specificity. Id.

The examiner rejected all claims as being unpatentable for reasons of obviousness. The rationale for the rejection was articulated as follows:

> Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 RT gene provided by Thimmig et al. (1993), as an Lpp-OmpA-RT fusion protein, as suggested by Georgiou et al. (1994), since Hone and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. The skilled worker would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 RT-specific immunological reagents (i.e., antibodies) which can be employed in a diagnostic, immunological, or biochemical assays.

Answer, pages 10-11.

In traversing the rejection, Appellant made several arguments. First, Appellant stated that "the references have not been shown to be combinable and no prima facie rejection made on this record." Brief, page 13, lines 18-23. Secondly, it was argued that there is no reasonable expectation of success that the claimed antigens, when expressed in attenuated bacteria and administered to a host, would produce both a

humoral and a cellular response. Id., pages 14-15. Finally, Appellant urged that not all the limitations of the claims were taught by the cited references since none mentioned the generation of both a humoral and cellular immune response to an HIV-1 reverse transcriptase or transactivating protein. Id., page 16.

We have no doubt that the skilled worker would have recognized the Hone publication as relevant to the claimed subject matter for its teaching of live oral Salmonella HIV-1 vectors for eliciting a specific immune response to HIV antigens. Because the publication does not describe the antigen as a HIV-1 reverse transcriptase or transactivating protein, it is not anticipatory. The next step therefore is to address whether it alone, or in combination with other references, would have made the claimed subject matter obvious. Every prior art reference casts its own peculiar shadow that extends its teachings beyond what is exactly disclosed in it, and into the realm of what it reasonably suggests to one of ordinary skill in the art. What is obvious from the teachings of the prior art is properly determined by applying the appropriate and objective legal standard of obviousness.

"When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness." In re Sang Su Lee, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002). A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art. "[T]he teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. The test for an implicit showing is what the

combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Kahn, 441 F.3d 977, 987-988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

After applying the proper standard of obviousness to the record before us, we cannot find the motivation to have replaced gp120 as described by Hone with an HIV reverse transcriptase. Hone's system is expressly characterized as a system for developing vaccines against HIV.

> [W]e constructed Salmonella strains that express rgp120 on the surface of the vector. Preliminary data suggest that surface-expressed rgp120 is significantly more immunogenic in both the mucosal and systemic compartments than cytoplasmic rgp120. These results, therefore, support the proposal that Salmonella vectors will be a safe and inexpensive means for delivery of HIV antigens to, and the elicitation of HIV-specific T cells in, the mucosal and systemic compartments.

Hone, page 203, "Abstract"

Thimmig is concerned with characterizing the activity of the p51 and p66 subunits of HIV reverse transcriptase. We do not find any disclosure in Thimmig that would have motivated the skilled worker to have adopted Hone's vaccine system to express HIV RT. We recognize that the skill in the art was high, and that an explicit suggestion to have utilized Hone's system is not required to establish prima facie obviousness. Nonetheless, the examiner's explanation that skilled worker would have been motivated to have selected Hone's system to "facilitate the development of HIV-1 RT-specific immunological reagents" is inadequate. Answer, pages 10-11. We agree with the examiner that HIV is medically important, but we don't see how this would be "sufficient motivation to prepare RT fusion constructs" for the purpose of making antibodies, when the Hone system is for making vaccines. Id., page 17. Thimmig describes anti-RT

antibodies. Thimmig, page 16533, column 1. Thus, "HIV-1 RT-specific immunological reagents" were already available in the prior art.

Georgiou does not compensate for these deficiencies because, like Hone, the patent only discloses the use of gp120 in a live bacterial vaccine, but not other HIV antigens. As we understand the Hone reference, the authors have described a system to express HIV antigens on the bacterial cell surface to develop live vaccines. The key element, in our view, which is lacking is the motivation to have expressed HIV reverse transcriptase or a transactivating protein on the surface of cells in a vaccine expression system. Both proteins are normally expressed inside host cells, unlike gp120 which is exposed extracellularly. There were no findings provided by the examiner to support the conclusion that, among the many available expression systems, the skilled worker would have been motivated to have selected Hone's system for intracellularly produced antigens. In particular, we see no discussion in the record as to whether RT was a target for vaccine development that would have made it an obvious replacement for gp120. To establish obviousness, there must be some teaching, suggestion, or motivation to combine the references. In re Rouffet, 149 F.3d 1350, 1355-1356 (Fed. Cir. 1998). Because the motivation is deficient, we conclude that a case of prima facie obviousness has not been established by the examiner. The rejection is therefore reversed.

Appellant primarily centered its argument on whether there would have been a reasonable expectation of success to develop a cellular immune response to RT when a host cell exhibiting the claimed characteristics is administered to an animal. Id., pages 14-15. It is not necessary for us to decide this issue at this time since we have found

motivation to combine the references lacking. Nevertheless, we note that Hone was confident enough that a measurable cellular response would occur to state, in the absence of concrete data, that "it is reasonable to propose, therefore, that Salmonella bearing surface-expressed rgp120 will elicit gp120-spcific CD8+ CTLs." Hone, page 206, column 2. Brey, cited in another rejection (below), describes substantially the same system used by Hone for its particular advantage in producing cell-mediated immunity. Brey, column 7, lines 5-15.

Brey in view of Georgiou and Thimmig

Claims 6, 8-10, 12, and 13 stand rejected under 35 U.S.C. § 103(a) as obvious over Brey[4] in view of Georgiou and Thimmig.

The Brey patent is directed to substantially the same vaccine expression system as disclosed by Hone, but for vaccinating animals against malaria. Brey, Abstract. This reference does not provide any motivation to have utilized the system for HIV-1 reverse transcriptase or transactivating protein as required by claim 6. For the same reasons as described above, the examiner has failed to establish prima facie obviousness of the claimed subject matter. This rejection is reversed.

Other Issues

Appellant's specification discusses prior art that describes a T-cell response to HIV-specific antigens in patients infected with HIV. Specification, page 4, line 21-page

[4] Brey et al. (Brey), U.S. Pat. No. 5,112,749, issued May 12, 1992

5, line 10. In this context, it is also stated that RT "was shown to be a target for cytotoxic T lymphocytes in infected humans (Walker, 1988, Lieberman, 1992, Rowland-Jones, 1995)." Id., page 14, lines 1-5. Furthermore, it is acknowledged in the application that "recent work has focused on using internal viral proteins as antigens, as opposed to envelope proteins, in the hopes of inducing a cell-mediated response." Id., page 14, lines 12-14. See also, id., page 4, lines 6-7. Both RT and the transactivating protein are internal antigens. Upon return of the application to the technology group, the examiner should consider whether the prior art described by Appellant in their patent application would have provided adequate motivation, with a reasonable expectation of success, for the skilled worker to have expressed reverse transcriptase or transactivating protein in the vaccine system described by Hone.

Summary

The rejections of claims 6, 8-10, 12, and 13 are reversed.

REVERSED

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